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CAMPELL, B	
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DATE MAILED: 10/09/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 7/19/96 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ——— days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☑ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ ____________________.

Part II SUMMARY OF ACTION

1. ☑ Claims 1-36 are pending in the application.

   Of the above, claims ____________ are withdrawn from consideration.

2. ☐ Claims ____________ have been cancelled.
3. ☐ Claims ____________ are allowed.
4. ☑ Claims 1-36 are rejected.
5. ☐ Claims ____________ are objected to.
6. ☐ Claims ____________ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on ____________. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on ____________. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed ____________, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. ____________ ; filed on ____________.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

The application should be reviewed for errors. For example, at p. 36 of the specification lines 29-31 are garbled. In claim 29, at line 3, it appears that "a" has been omitted after "to." Please make appropriate correction of these and all similar errors.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to make and use the invention, i.e. failing to provide an enabling disclosure.

The specification does not teach how to use the methods of claims 1-11, which recite that the rate of transcription of a gene is increased. This is not what occurs in the process disclosed in the specification. The specification discloses a process in which a gene is transfected into a cell, where it is constitutively expressed. Furthermore, a constitutive promoter is defined as a promoter which is not under environmental control (specification, p. 14). How, then, is one to increase the rate of transcription from a promoter that, by definition, is unaffected by external factors which one might manipulate? This aspect of the objection could be overcome by amending the claims to recite that a gene under control of a constitutive promoter is transfected into and expressed in the cell.

Even if the above concerns were satisfied, the specification would still not be enabling for the full breadth of the claims for the following reasons.

The specification does not teach a method for transfection by TILs as recited in claims 8 and 19. Applicants' argument citing Culver et al. is not persuasive. This reference does <u>not</u> demonstrate that DNA is transferred from TILs to other cells as required by the claims. A gene may get into a tumor by the method of Culver et al., but it remains in the TIL.

DJL

Claims 1-28 and 35 encompass *in vivo* methods utilizing any means of administering the DNA construct. The specification is enabling for *in vitro* transfection methods. With regard to *in vivo* methods, however, the specification only enables the use of methods wherein the DNA (or viral vector containing same) is injected directly into the site where transfection is desired. Viral vectors tend to accumulate in certain tissues. For example, adenoviruses and herpes viruses have tropisms for liver and neuronal tissues, respectively (Herz et al., Breakefield et al.). Liposomes also tend to accumulate in particular tissues when injected intravenously. One would not expect intravenous administration of adenovirus which results in transfection of liver cells to aid in treatment of prostate cancer, for example. The admitted problems associated with systemic administration of TNF (specification, p. 3) further argue for the importance of targeting gene expression. The specification does not teach how to target DNA or viral vectors to particular tissues so that an effective level of expression of the transfected DNA is achieved. Marshall states that "there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (p. 1050, col. 1) and that "difficulties in getting genes transferred efficiently to target cells - and getting them expressed - remain a nagging problem for the entire field" (p. 1054, col. 3). James Wilson, one skilled in the art, is quoted as saying that "'[t]he actual vectors - how we're going to practice our trade - haven't been discovered' yet" (p. 1055, col. 2). Culver et al., reviewing gene therapy for cancer, conclude that the "primary factor hampering the widespread application of gene therapy to human disease is the lack of an efficient method for delivering genes *in situ*, and developing strategies to deliver genes to a sufficient number of tumor cells to induce complete tumor regression or restore genetic health remains a challenge" (p. 178). Hodgson discusses the drawbacks of viral transduction and chemical transfection methods, and states that "[d]eveloping the techniques used in

OK

animal models, for therapeutic use in human somatic cells, has not been straightforward" (pp. 459-460). Miller et al. also review the types of vectors available for *in vivo* gene therapy, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances....targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (p. 198, col. 1). Since effective DNA targeting and delivery are not routinely obtainable by those skilled in the art, and the specification does not teach other methods, the specification is enabling only for direct injection of DNA or virus.

Regarding claims 1-30 and 35, the specification does not adequately teach how to use *in vivo* methods requiring expression of genes other than the tumor necrosis factor α (TNF) gene, or pharmaceutical compositions comprising other genes. Most cytokines have pleiotropic effects; they interact with each other and with various biochemical pathways (Arai et al., p. 785). One skilled in the art can not predict the outcome of expressing any and all cytokines in a mammal, because the intact animal is much more complicated than *in vitro* systems. The specification does not adequately teach which cytokines will have protective effects or which will have sensitizing effects. The systemic effects of expressing any cytokine are unpredictable, particularly if expression is not confined to any particular location.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to make and use the full scope of the claimed invention. This is particularly true given the breadth of the claims, the amount of experimentation necessary, the nature of the invention, the state of the prior art, the scarcity of guidance regarding non-exemplified embodiments, and the unpredictable nature of the art.

Claims 1-30 and 35 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-28, 35 and 36 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 1, 18 and 26 are grammatically incorrect in their recitation of "radioprotecting a cell to." OIL

Claim 1 is incomplete because it lacks a final step for achieving radioprotection or radiosensitization. The biological response requires increased accumulation of the factor, which is not ensured by merely increasing the rate of transcription.

Claims 6, 14, 17, 25 and 28 are indefinite and confusing in their use of "and" in the Markush group. It is not clear whether this means that SV40 early and late are one promoter, SV40 early is meant to be paired with any of the following promoters, etc. Furthermore, "actin" is a protein, not a promoter. "EBV origin of replication" appears to be a location, not a promoter. Finally, it is not clear what the difference is between "SV40" and "SV-40."

Claims 9 and 20 are incorrect in their recitation of "the liposome is DOTMA...", which should read "the liposome comprises..." Pure lipid does not form liposomes. OIL

Claims 12, 23 and 26 are incorrect in their recitation of "secretes a cytokine in a mammalian cell" because if a cytokine remains in a cell, it is not secreted. OK

Claims 13, 24 and 27 are confusing because it appears that the entire vector is under control of the recited promoter, not just the cytokine expressing region. OK

Claim 18 is incomplete because it lacks a final step wherein the gene construct is expressed and the cell is protected. Also, it appears that step (c) is not required for the method to operate. OK

Claim 35 is incomplete because it is not clear that the transfected DNA is expressed, which is required for the method to be operative. OK

Claim 36 is incomplete because it is not clear that the transfected DNA is expressed, which is required for the method to be operative. Furthermore, claim 36 lacks a final step of assessing the cells' response. OK

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-7, 15-18, 29, 31, 33, 35 and 36 are rejected under 35 U.S.C. § 103 as being unpatentable over Hallahan et al. (C15) in view of Teng et al. (C33), Neta et al. (C21) and Vile et al. Hallahan et al. show that TNF and ionizing radiation act synergistically to kill human tumor cells *in vitro* (entire document). Hallahan et al. report that cell killing is maximized by addition of TNF 4-12 hr prior to irradiation, i.e. the TNF sensitizes tumor cells to the effects of radiation (p. 73, col. 2). Hallahan et al. disclose

that TNF enhances the effect of radiation in mice *in vivo*, and suggest clinical use of TNF in combination with radiation (p. 74). Hallahan et al. do not disclose methods in which a TNF gene is transfected into cells to sensitive or protect tumorous and normal cells, respectively, prior to irradiation. Teng et al. disclose experiments in which murine tumor cells were transfected with the human TNF gene under control of the CMV intermediate early promoter, then implanted into nude mice (entire document). Teng et al. show that transfected tumor cell lines which produce moderate levels of TNF grow more slowly than non-transfected cell lines when implanted, and that this level of TNF production does not cause serious weight loss (e.g. Table 1). Neta et al. teach that TNF can simultaneously radiosensitize tumor cells and radioprotect normal cells (pp. 391-392; p. 394, col. 2). Vile et al. teach a method for transfecting tumor cells and surrounding normal cells *in vivo* by direct injection of DNA into a tumor (pp. 965-966).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the tumor cell killing method of Hallahan et al. by transfecting tumor cells with the TNF gene as taught by Teng et al. rather than administering TNF directly. One of ordinary skill in the art would have expected that normal cells would be radioprotected by this method, given the teachings of Neta et al. and the knowledge that the DNA injection method of Vile et al. would transfect adjacent normal cells as well as tumor cells. There would have been a reasonable expectation of success, given the finding that TNF produced by a transfected tumor can suppress tumor growth without causing severe systemic side effects, as taught by Teng et al. One of ordinary skill in the art would have been motivated by the explicit suggestion of Hallahan et al. to use the combination of radiation and TNF *in vivo*, and by the readily apparent advantage of supplying TNF locally without causing cachexia as taught by Teng et al. Furthermore, claims 1-7, 15-18 and 36 encompass transfection of cultured cells. There was an even greater

expectation that transfected, cultured cells expressing TNF would be successfully radiosensitized or radioprotected (depending on the type of cell), given the *in vitro* data of Hallahan et al. With regard to claim 31 (and subsequent dependent claims), the claim requires only that the TNF be expressed, not that any therapeutic benefit be obtained. There was at least a reasonable expectation that TNF would be expressed *in vivo* by transfecting cells with the gene construct of Teng et al. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 9, 19 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. as applied to claims 1-7, 15-18, 29, 31, 33, 35 and 36 above, and further in view of Felgner et al. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. teach a method for radioprotecting and/or radiosensitizing cells prior to irradiation, as discussed above. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. do not teach a method wherein the DNA construct is administered in liposomes. Felgner et al. teach liposome compositions for administering DNA to animals *in vivo* (e.g. col. 8). Felgner et al. teach that the disclosed lipids provide more effective intracellular delivery (col. 8, line 66-68).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. by injecting the DNA in a liposome preparation as taught by Felgner et al. One of ordinary skill in the art would have been expected this modification to increase the efficiency of DNA delivery as taught by Felgner et al. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 10, 12-14, 19, 21, 23-28, 30 and 32 are rejected under 35 U.S.C. § 103 as being unpatentable over Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. as applied to claims 1-7, 15-18, 29, 31, 33, 35 and 36 above, and further in view of Herz et al. (C18). Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. teach a method for radioprotecting and/or radiosensitizing cells prior to irradiation, as discussed above. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. do not teach a method wherein the DNA construct is administered as an adenoviral vector. Herz et al. show that an adenoviral vector can be used to transiently express heterologous DNA under control of the CMV promoter in mice (entire document). Herz et al. show that intravenous administration of the virus results in transfection of hepatic parenchymal cells (p. 2815).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. by administering the TNF gene in an adenoviral vector as taught by Herz et al. One of ordinary skill in the art would have been motivated to do so in order to target liver parenchymal cells, for example. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 11, 19, 22, 30 and 32 are rejected under 35 U.S.C. § 103 as being unpatentable over Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. as applied to claims 1-7, 15-18, 29, 31, 33, 35 and 36 above, and further in view of Breakefield et al. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. teach a method for radioprotecting and/or radiosensitizing cells prior to irradiation, as discussed above. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. do not teach a method wherein the DNA construct is administered as a HSV vector. Breakefield et al.

teach that HSV vectors can be used to express heterologous DNA in neurons (pp. 211-213).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. by administering the TNF gene in a HSV vector as taught by Breakefield et al. One of ordinary skill in the art would have been motivated to do so in order to transfect neuronal cells. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claim 34 is rejected under 35 U.S.C. § 103 as being unpatentable over Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. as applied to claims 1-7, 15-18, 29, 31, 33, 35 and 36 above, and further in view of Mattern et al. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. teach a method for radioprotecting and/or radiosensitizing cells prior to irradiation, as discussed above. Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. do not teach a method wherein the DNA construct is administered to a human subject. Mattern et al. teach that human tumor xenografts are an art-accepted model for human cancer (entire document).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to extend the methods of Hallahan et al. in view of Teng et al., Neta et al. and Vile et al. to human patients. There would have been a reasonable expectation of success, given the fact that TNF and radiation were known to have a synergistic effect on human tumor cells as taught by Hallahan et al., and given the knowledge that the nude mouse model of Teng et al. was expected to reasonably model human cancer as taught by Mattern et al. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-7, 15-18, 29, 31 and 33-35 are rejected under 35 U.S.C. § 103 as being unpatentable over Hallahan (C16) in view of Teng et al. and Vile et

al. Hallahan et al. disclose phase I clinical trials in which TNF was administered to patients prior to radiation treatment (entire document). Hallahan et al. teach that enhancement of tumor control and radioprotection have been demonstrated *in vivo* when TNF is administered prior to irradiation. Hallahan et al. specifically suggest trials of "TNF gene therapy localized to tumors in combination with radiation." Hallahan et al. do not teach materials and methods for "TNF gene therapy." Teng et al. disclose experiments in which murine tumor cells were transfected with the human TNF gene under control of the CMV intermediate early promoter, then implanted into nude mice (entire document). Teng et al. show that transfected tumor cell lines which produce moderate levels of TNF grow more slowly than non-transfected cell lines when implanted, and that this level of TNF production does not cause serious weight loss (e.g. Table 1). Vile et al. teach a method for transfecting tumor cells and surrounding normal cells *in vivo* by direct injection of DNA into a tumor (pp. 965-966).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to transfect tumor cells with a gene encoding TNF prior to radiation therapy, as suggested by Hallahan et al. It would have been obvious to use the CMV/TNF construct of Teng et al., transfecting by direct injection as taught by Vile et al. There would have been a reasonable expectation of success, given the known radiosensitizing and radioprotecting effects of TNF as taught by Hallahan et al., the demonstrated efficacy of the construct of Teng et al., and the expectation that both tumor and normal cells would be transfected by injection as taught by Vile et al. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Claims 8, 9, 19 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Hallahan et al. in view of Teng et al. and Vile et al. as applied to claims 1-7, 15-18, 29, 31 and 33-35 above, and further in view of

Felgner et al. Hallahan et al. in view of Teng et al. and Vile et al. teach a method for radioprotecting and/or radiosensitizing cells prior to irradiation, as discussed above. Hallahan et al. in view of Teng et al. and Vile et al. do not teach a method wherein the DNA construct is administered in liposomes. Felgner et al. teach liposome compositions for administering DNA to animals *in vivo* (e.g. col. 8). Felgner et al. teach that the disclosed lipids provide more effective intracellular delivery (col. 8, line 66-68).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Hallahan et al. in view of Teng et al. and Vile et al. by injecting the DNA in a liposome preparation as taught by Felgner et al. One of ordinary skill in the art would have been expected this modification to increase the efficiency of DNA delivery as taught by Felgner et al. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

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It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Hallahan et al. in view

of Teng et al. and Vile et al. by administering the TNF gene in an adenoviral vector as taught by Herz et al. One of ordinary skill in the art would have been motivated to do so in order to target liver parenchymal cells, for example. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

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It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the methods of Hallahan et al. in view of Teng et al. and Vile et al. by administering the TNF gene in a HSV vector as taught by Breakefield et al. One of ordinary skill in the art would have been motivated to do so in order to transfect neuronal cells. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce Campell, whose telephone number is 703-308-4205. The examiner can normally be reached on Monday-Thursday from 8:30 to 5:00 (Eastern time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached on 703-308-2035. The FAX phone number for art unit 1819 is 703-308-0294.

An inquiry of a general nature or relating to the status of the application should be directed to the group receptionist whose telephone number is 703-308-0196.

Bruce Campell
October 7, 1996

BRUCE R. CAMPELL
PRIMARY EXAMINER
GROUP 1800